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Neurotransmitter, antioxidant and anti-neuroinflammatory mechanistic potentials of herbal medicines in ameliorating autism spectrum disorder

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Abstract: ***Background***: Autism spectrum disorder (ASD) is a neurodevelopmental issue that disrupts behavior, nonverbal communication, and social interaction, impacting all aspects of an individual's social development. The underlying origin of autism is unclear, however, oxidative stress, as well as serotonergic, adrenergic and dopaminergic systems are thought to be implicated in ASD. Despite the fact that there is no effective medication for autism, current pharmacological treatments are utilized to ameliorate some of the symptoms such as selfmutilation, aggression, repetitive and stereotyped behaviors, inattention, hyperactivity, and sleep disorders.

Methods: In accord with the literature regarding the activity of herbal medicines on neurotransmitter function, we aimed to review the most worthy medicinal herbs possessing neuroprotective effects.

Results: Based on the outcome, medicinal herbs such as Zingiber officinale, Astragalus membranaceu, Ginkgo biloba, Centella asiatica and Acorus calamus, have antioxidant activity, which can influence neurotransmitter systems and are potentially neuroprotective.

Conclusion: Consequently, these herbs, in theory at least, appear to be suitable candidates within an overall management strategy for those on the autism spectrum.

Keywords: Autism spectrum disorder, Herbal medicine, inattention, Neurotransmitters, Nervous system,

1. INTRODUCTION

Autism is a neurodevelopmental disorder characterized by deficits in social communication and interaction. It can be termed autism spectrum disorder (ASD) such that symptoms are classified into various types and degrees. Signs of autism commonly appear in infants of two or three years of age and certain developmental impediments may occur even earlier. Children suffering from ASD display different attitudes and emotions compared to subjects of comparable age and it is a lifelong developmental disorder. However, early intervention may subsequently lead to improved

outcome and an educational program at a young age may well help individuals to have a moderately productive life with their own choices (1).

Although the etiology of autism has remained unknown, environmental and genetic factors can modify the condition in terms of symptoms and severity. In extreme cases, autistic individuals become isolated and neglected and some clinical psychologists believe that cognitive impairment augments any deficiency in social skills. The primary problem resides in executive performance leading to insufficiencies in problem solving and action planning impeding their attention. All these deficits have a negative impact on the ability of individuals to function properly in social activities. Secondly, it has been suggested that people on the autism spectrum are not able to understand typical states of mind, so they cannot recognize and predict the intentions of others (2, 3).

The prevalence rate of autism varies in different cultures and ethnic groups. It has been estimated for instance in the USA, that one out of every sixty-eight children (~1.5%) are on the autism spectrum although an incidence of six per thousand (0.6%) has also been indicated. What is more, the ASD prevalence rate differs by gender and boys are thought to be affected 4.2 times more than girls. However, female subjects tend to have greater cognitive impairment and show more atypical behaviors. Such differences in occurrence frequency probably result from a disparity in symptom expression (4-6). The problem of managing ASD is that individuals are invariably focused on a confined number of objects and events. Many have considerable communication problems, and constantly need support. Therapeutic interventions are usually limited to behavioral and drug therapies and most behavioral training programs try to create self-help, social and communication skills. Drug treatment is aimed at reducing and controlling problematic behaviors such as isolation, aggression and self-harm. Antiepileptic drugs are widely employed for ASD to reduce repetitive and stereotypical behaviors, social isolation and aggression as well as difficult behaviors such as hyperactivity, severe bitterness, mood swings and self-harm. However, some children do not respond positively to these drugs (7-11) and investigations have indicated both positive and negative effects of certain foods or plants, like Gingko, especially in combination with conventional treatments. The present review therefore aims to present herbal medicines that alleviate the signs and symptoms of autism highlighting their possible mechanisms (11).

2. AUTISM PATHOPHYSIOLOGY

The cause of autism has remained unknown, but ASD may occur concomitantly to several other genetic disorders. The characteristics of autism are clearly associated with a number of chromosomal aberrations, such as chromosomal proliferation, chromosomal removal, and reversal of chromosomes. Nonetheless, chromosomal abnormalities account for only 10% of cases of ASD. Transmission of autism symptoms is not attributable to just one gene alone, but it

is more likely that it is a complex condition to which 15 different genes contribute. There is also a family relationship between autism disorder and other psychological problems. Evidence suggests that social, linguistic and psychological problems in autism disorders usually have a family background. Pregnancy and childbirth problems have been identified as important non-genetic factors for the development of ASD. Consumption of drugs such as thalidomide and valproate during pregnancy as well as bleeding after the first trimester are chief environmental factors for autism development. Autopsy and fMRI analysis have provided insights into the relationship between autism and brain abnormalities. Post-mortem autopsies upon individuals on the autism spectrum have revealed that there are abnormalities in some parts of the brain such as the cerebellum and limbic system. Cerebellar abnormalities are related to movement impairments, including a lack of balance, manual skill defects and problems in hand movements. In addition, autopsy studies indicate that brain size in autism has a tendency to be larger than normal and such malformations initially occur during embryonic development (12-17).

3. NUTRITION AND AUTISM

Nutritional factors, especially micronutrients are essentially involved in neurogenesis (18) and medications are used to improve symptoms of autism including hyperactivity, irritability, attention problems, aggression, repetitive behavior, anxiety and depression. It has also been demonstrated that vitamins B6 and B12, magnesium and selenium are additionally beneficial in ASD. In view of this, it is recommended that individuals on the autistic spectrum should eat magnesium rich foods such as soybeans, spinach, almonds, pumpkin seeds, sunflower seeds, lentils, barley and broccoli. Furthermore, the consumption of cereals and brans can provide B group vitamins. Many studies have confirmed the positive effects of the Gingko plant by boosting memory and cognitive function while milk casein, gluten in certain foods and pasta exacerbate the symptoms of the condition. Likewise, canned and cooked foods, chocolate, artificial dyes and fast foods are also detrimental (3, 4). Acupuncture has been shown to possess value in ASD and physical exercise, as well as massage are of help. It has been reported that the levels of zinc, selenium, magnesium, vitamins A, B, C, D, E and carnitine (19, 20), are lower than normal in the blood and hair of children on the autism spectrum. Moreover, low levels of vitamin D (21) and folic acid (22) during pregnancy are major risk factors for the development of autism. In consequence, such outcomes emphasize the significant part nutrients play in ASD. In this regard, a double-blind trial disclosed a substantial improvement of symptoms in 3–12 year old children exhibiting autism (23). Another study on 3–8 year old autistic children receiving mineral supplements and multi-vitamins divulged improvements in receptive language and general behavior (24). In other conditions such as attention deficit hyperactivity disorder (ADHD) in children, vitamin B6 and magnesium also improves hyperactivity and hyperemotivity/aggressiveness accentuating the therapeutic usefulness of an Mg-B6 regimen (25).

The composition and level of plasma and red blood cell fatty acids, particularly the concentration of omega-3 fatty acids (26), is essential to neural development. Therefore, consumption of fatty acids may be beneficial in ASD. In this regard, women who consumed higher levels of polyunsaturated fatty acids (PUFA) during pregnancy had a reduced risk of having children with autism in comparison to those with a lower PUFA intake. Additionally, the results of another study showed that consumption of omega-3 fatty acids (1.0 g daily) in 7–18 year old autistic children, significantly improved attention problems and core symptoms of their autism (27).

4. AUTISM AND NEUROTRANSMITTER SYSTEMS

Results of research support the assumption that autism disrupts synaptogenesis, and a number of neurotransmitter pathways may also play a part in susceptibility to autism. In this respect, based on various pathophysiological and genetic findings, neurotransmitter mechanisms and neurotrophic factors have been suggested as being involved in ASD. Serotonin and dopamine are monoamine neurotransmitters engaged in the modulation of adult cortical plasticity and are believed to play a vital role in the growth of the early cortex by controlling, migration and neuronal diversity. Serotonin functions through seven known receptor families (5-HT1 – 5-HT7) and is associated with homeostasis of sleep, emotions, awareness, learning, muscle mobilization, and endocrine functions. Dopamine operates via five receptor types (D_1 – D_5) and modifies various cognitive functions including reward, motivation, memory, awareness as well as problem solving and it is also critical in the control of voluntary movement. The metabolism of these two neurotransmitters is both complex and tissue-specific. In central neurons, serotonin is biosynthesized from tryptophan precursor in sequence by tryptophan hydroxylase then aromatic acid decarboxylase enzymes but it is catabolized by monoamine oxidase A (MAO-A). In contrast, dopamine is sequentially biosynthesized from tyrosine precursor by tyrosine hydroxylase then DOPA decarboxylase enzymes and it is subsequently broken down by both monoamine oxidase B (MAO-B) and catechol-O-methyltransferase (COMT).

The outcome of extensive research indicates that both serotonergic and dopaminergic systems can be regarded as powerful candidate mechanisms involved in autism. Firstly, high blood and urine serotonin concentrations have been reported in roughly one-third of persons with autism, while normal peripheral dopamine levels have been recorded in ASD. Secondly, selective serotonin reuptake inhibitors (SSRIs) and dopamine receptor antagonists are inclined to diminish autism-related symptoms which include aggression, self-injury, and maladaptive behavior. Thirdly, positron emission tomography (PET) neuroimaging studies have unveiled an atypical serotonin synthesis imbalance in frontal, temporal and parietal cortices in autism. Moreover, dopaminergic activity appears to be changed in the anterior, medial, and prefrontal cortical regions in subjects with autism (28-31). In addition, studies have shown that other systems such as adrenergic, cholinergic and opioid neurotransmitter pathways plus glucocorticoids as well as

amino acid neurotransmitters can participate in the pathophysiology of autism. Noradrenaline itself does not appear to be a participant initiating the signs of ASD. However, α-$_2$ adrenoceptor agonists such as clonidine which reduce noradrenaline function, are capable of managing hyperactivity in young persons with autism and yet these drugs have no effect on the core symptoms. β-adrenoceptor blockers on the other hand, are effective in controlling aggression, self-mutilation, and febricity (32). In regard to the cholinergic system, a substantial reduction in muscarinic receptors in the cerebral cortex and a nicotinic receptor deficit has been recorded in the post-mortem brains of individuals with autism. Nevertheless, it is not evident how these variations relate to the causes of autism though the reduced effectiveness of nicotinic receptors might suggest that medicinal products with nicotinic agonist activity would boost attention (33).

5. OXIDATIVE STRESS AND AUTISM

Autism is associated with oxidative stress which is linked with excitotoxicity, impaired energy metabolism, inflammation, membrane lipid abnormalities and aberrant immune response. The markers of lipid peroxidation are increased in autism, indicating that oxidative stress (OS) might be associated with autism. The level of OS is evaluated by measuring the products of lipid peroxidation, glutathione and other antioxidants which act against reactive oxygen species (ROS). Also, membrane phospholipids, which are considered as prime targets for ROS, are usually altered in autism. In comparison to unaffected siblings, phosphatidylserine level in erythrocyte membrane of autism children is increased and phosphatidylethanolamine level is decreased. Antioxidant enzymes or their activities including glutathione peroxidase, superoxide dismutase and catalase in autism patients are decreased. Moreover, in autism, genetic and environmental factors may enhance the vulnerability to oxidative stress. These findings suggest the involvement of oxidative stress in the development of autism. Therefore, medicinal plants with antioxidant activity might be beneficial in these patients [34].

6. AUTISM AND MEDICINAL PLANTS

Herbal medicines have been studied and yielded encouraging outcomes in the therapy of a broad range of health complications involving cardiovascular and neurological issues (35, 36) in addition to diabetes mellitus (37, 38). These types of treatment can have reduced side effects and may even decrease the side effects of other agents such as gentamicin (39). Diagnosis of ASD is difficult since there is no widely available medical test and it is largely dependent on behavioral assessment and identification of developmental delay. There is an ancient Chinese term in which a condition could conceivably be equated with modern-day autism and it was defined as "Phlegm in the heart orifice". During ancient times, there were not only alternative herbal treatments available, but also acupuncture was freely used, although even nowadays, medicinal plant therapeutic mechanisms are often unclear and potential toxicity is an ever-present problem (40). Unfortunately, the number of studies intended to evaluate the activity of medicinal plants on autism is scarce. In respect of this, herbal medicines with neuroprotective effects have potential

as remedies for treating the signs of autism (41). The most noteworthy of these remedies are outlined below.

7. *ZINGIBER OFFINIALE*

Zingiber officinale (Ginger), which contains gingerol, paradols and shogaol, belongs to the Zingiberaceae family. It has been established that consumption of *Z. officinale* has antioxidant activity, an acetylcholinesterase inhibitory effect (AChEI), and neuroprotective as well as memory-enhancing properties. It is traditionally used to reduce the signs of autism and it is the plant root that is utilized for its neuroprotective capacity on ASD (42). In an experimental rodent model of age-related dementia, *Z. officinale* disclosed efficacy in enhancing memory and increasing hippocampal neuronal density (43). Equally, in rats with focal cerebral ischemia, *Z. officinale* decreased brain infarct volume after unilateral middle cerebral artery occlusion and it induced a cognitive improvement which was partly ascribable to an antioxidant action (44).

Significant antioxidant effects of a 6-gingerol-rich fraction of *Z. officinale* and a protective action against the cerebral cortical damage induced by the neurotoxin acrylonitrile have been reported. Hence, this component of the plant extract counteracted the depletion of central glutathione as well as the activities of glutathione peroxidase (GPX), glutathione S-transferase (GST) and superoxide dismutase (SOD) caused by acrylonitrile. It also reestablished levels of nitric oxide, malondialdehyde (MDA) and the pro-inflammatory cytokines interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α) which were raised by the neurotoxin (45).

8. *ASTRAGALUS MEMBRANACEUS*

Astragalus belongs to the legume family Fabacae and is frequently known as milkvetch. It has two commonplace species (*Astragalus membranaceus* and *Astragalus mongholicus*), which have been used in Eastern traditional medicine for many years. *Astragalus membranaceus* contains cycloartane-type triterpene glycosides that are utilized for their anti-inflammatory-, antioxidant-cardioprotective- and immune system stimulating activities. *A. membranaceus* has been used as an herbal remedy to treat general weakness as well as chronic illness, and to increase overall vitality. An extract of the other common species, *Astragalus mongholicus*, has been shown in moderate doses, to possess anticonvulsant properties in a rodent model and may be beneficial in convulsive disorders (46).

The *A. membranaceus* plant elevates the resistance of dopaminergic neurons to neurotoxins. As a consequence, in a Parkinson's disease primary nigral cell culture model, the neurotoxin 6-hydroxydopamine gradually becomes neutral following pretreatment with astragaloside IV extracted from the *A. membranaceus* root (47). In addition to this, the polysaccharide astragalan,

present in *A. membranaceus*, is capable of attenuating aging and proteotoxic stress pathways by reducing aggregation-prone proteins and a global disruption of proteostasis (48).

In peripheral nerve studies in rats, concentrations of astragaloside evoked a higher rate of sciatic nerve regeneration, improved numbers of myelinated axon growths plus greater evoked action potentials than corresponding controls. This activity was subject to a biphasic concentration-effect relationship since there was a completely opposite effect which terminated nerve anastomosis at a higher concentration (49). In a later investigation, an aqueous extract of *A. membranaceus* was reported to augment a nerve growth factor promoted outgrowth of neurites in PC12 cells and this was further evidence for the regenerative and growth enhancing neuronal activity of *A. membranaceus* (50). Once again, it would appear that it is the neuroprotective propensity present in the commonly employed aerial parts of the plant that contributes to its utility in traditional medicine (42)

9. *CENTELLA ASIATICA*

Centella asiatica (CA) is a traditional medicinal herb that belongs to the Apiaceae family and it is known as Pegaga in Malaysia or Goto kola in traditional Chinese and Ayurvedic medicine. *C. asiatica* grows in tropical swampy areas in many regions of the world but is native to India, China, Sri Lanka, Madagascar, Indonesia and Malaysia. The therapeutic activity of *C. asiatica* is clearly related to a wide range of active constituents including pentacyclic triterpene derivatives, polyphenols, alkaloids, glycosides and flavonoids (51). Over thousands of years, it has been extensively used in folk medicine; and currently, it has been incorporated into modern medicine for its antitubercular, antileprotic, memory enhancing, antitumor and wound healing characteristics (52). Tiwari et al., reported that due to its cholinergic, antioxidant and anti-neuroinflammatory activities, there was a significant improvement in elderly patients with mild cognitive impairment arising from 6-month administration of *C. asiatica* (53). There are an increasing number of studies focusing on the neuroregenerative and brain supporting capacities of *C. asiatica*. Gray et al., described a positive effect of an aqueous *C. asiatica* extract which raised the expression of Synaptophysin and PSD95 synaptic markers in the hippocampus and frontal cortex of old and young mice (54). Synaptophysin and PSD95 are pre- and post-synaptic markers of spine density known as a structural basis for changes in cognition.

C. asiatica has also been used to treat Alzheimer's disease (AD) which is characterized by a decline in cognitive function. There are two hypotheses underlying the development of Alzheimer's disease. Firstly, there is thought to be a cognitive decline due to the degeneration of cholinergic neurons. Secondly, neuronal damage occurs due to the generation of neurotoxic Aβ peptide oligomers and fibrils which are associated with inflammation and oxidative stress leading to neuronal dysfunction ultimately followed by the central deposition of amyloid plaques. Ramesh et al., found that *C. asiatica* aqueous leaf extract did not inhibit Aβ peptide aggregation nor did it bring about the disintegration of preformed fibrils. Therefore, it was

speculated that apart from its antioxidant and anti-inflammatory properties, *C. asiatica* may act either by promoting α-secretase non-amyliodogenic processing of amyloid precursor protein (APP), or by inhibiting β-secretase (BACE1) thus preventing APP cleavage extracellularly and any subsequent formation of Aβ peptide (55). It has been demonstrated *in vitro*, that the triterpenoid saponin asiaticoside found in *C. asiatica* inhibits the phospholipase A_2 (PLA_2) subtypes $cPLA_2$ and $sPLA_2$ in cortical neurons. In light of this, stimulation of PLA_2 activity is crucial to the neurotoxicity of Aβ peptide which leads to apoptosis and neuronal death, so the medicinal plant and its constituents have been proposed as a potential treatment for neurodegenerative conditions (56). Since mitochondrial dysfunction and oxidative stress are associated with cognitive impairment, Gray and coworkers studied the activity of *C. asiatica* on these fundamental pathways. In essence, *C. asiatica* improved cognitive function and elicited an expression of several electron transport chain (ETC) genes in the hippocampus, frontal cortex, cerebellum and liver of both young and aged mice. The changes in gene expression were considered to be an action on mitochondrial biogenesis and in combination with stimulated antioxidant response genes, this might have been an underlying factor in the observed improvement in cognition (54).

Parkinson's disease has a molecular basis centered around mitochondrial dysfunction and oxidative stress characterized by loss of motor control due to disrupted central neurotransmission. In relation to this, *C. asiatica* counteracted 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) neurotoxin-induced Parkinsonian-like oxidative stress biomarker accumulation (lipid hydroperoxides, xanthine oxidase and protein carbonyl content) in rat corpus striatum and hippocampus. Similarly, *C. asiatica* extensively reversed a concurrent MPTP-incited decline in striatal and hippocampal total antioxidants, catalase, glutathione peroxidase and superoxide dismutase) (57). It was suggested therefore, that *C. asiatica* may well be an efficacious neuroprotective agent against neurodegenerative conditions typified by Parkinson's disease (57). Analogously, asiaticoside isolated from *C. asiatica* maintained dopamine metabolic balance by antagonizing MPTP-induced neurotoxicity to ameliorate motor dysfunction and manifest both neuroprotective and antioxidant properties (58).

Amongst a variety of active compounds in *C. asiatica*, asiatic acid (AA) not only hastens neuronal regeneration but also stimulates elongation of neurites (59). Likewise, there is evidence in favor of a protective capability of asiatic acid against C(2)-ceramide-induced cell death by antagonizing apoptosis that is contingent upon mitochondria (60). Besides asiatic acid, phenolic compounds in *C. asiatica* have been proposed to retain a distinct therapeutic potential for Alzheimer's disease treatment (61). Correspondingly, although *C. asiatica* lacked protective activity from oxidative damage and glutamate toxicity, administration of its aqueous extract in the Tg2576 AD transgenic Aβ peptide overexpressing mouse model ameliorated behavioral abnormalities associated with raised Aβ levels. In this instance, two major triterpene saponosides (madecassic acid plus asiatic acid mentioned above) and their heterosides; (asiaticoside and madecassoside) account for some of the positive effects of *C. asiatica* on the central nervous

system. Also in AD, there is a cholinergic deficit particularly in nucleus basalis of Meynert neurons and choline acetyl transferase activity is diminished leading to the biosynthetic deficiency of acetyl choline which correlates with impaired memory (62).

Acetylcholinesterase (AChE) hydrolyzes acetylcholine (ACh) i.e. its breakdown, so inhibition of AChE and the pseudocholinesterase enzyme butyrylcholinesterase (BChE), has been considered a potential target in drug development against AD and autism. Four inhibitors of AChE have been approved in AD treatment, namely, rivastigmine, tacrine, donepezil and galantamine which also stimulates nicotinic cholinergic receptors further increasing Ach release (63). Studies on these medications have divulged a potential usefulness for treating core and attendant ASD symptoms and further clinical trials have been advocated to substantiate their effectiveness in this respect (63). In the perspective of this outcome deduction, a hydroalcoholic extract of *C. asiatica* has a definite inhibitory effect on AChE activity *in vitro* (64). Further evidence supporting a positive action of *C. asiatica* in persons with autism derives from the finding that a flavonoid mixture of luteolin, quercetin and rutin, all of which are also present in *C. asiatica* (65, 66), has been shown to cause speech resumption in a trial with pediatric ASD participants (67).

Glutamic acid decarboxylase (GAD) is a rate limiting enzyme that converts glutamate to the central neurotransmitter gamma amino butyric acid (GABA). In postmortem autistic cerebellar and parietal cortices, GAD protein has been shown to be appreciably reduced and this may be attributable to aberrations in levels of glutamate/GABA or the density of central GABA transporters or its receptors in autism (68). The possible influence of *C. asiatica* on GABA biosynthesis has been studied and an extract of the medicinal plant actually enhanced glutamic acid decarboxylase (GAD) activity (69). It may be hypothesized therefore, that any reversal of ASD symptoms by *C. asiatica* may be ascribed at least in part to a rise in GAD activity.

To unravel the underlying mechanisms mediating *C. asiatica* actions, the MEP/ERK signaling pathway was regarded to be involved (59). In support of this, a neuritogenic effect of a standardised extract of *C. asiatica* (known as ECa 233) (70) has been shown to be mediated via ERK1/2 and Akt signaling pathways. Tyrosine kinase receptor activation triggers these molecular signals and several neurotrophic ligands such as nerve growth factor (NGF), brain derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3) have been identified. Hence, activation of MEK/ERK and PI/2K/Akt increases cell survival, neuronal growth and differentiation (71). There is evidence that the ERK/RSK signaling pathway is a mediator of *C. asiatica* in terms of its memory enhancing property. Essentially, *C. asiatica* was found to increase phosphorylation of cAMP response element-binding protein (CREB) in neuroblastoma cells expressing $A\beta_{1\text{-}42}$ (72). In a later study, an ethanolic extract of *C. asiatica* was reported to operate through the caspase-9 pathway (73). Indeed, treatment of l-buthionine-(S,R)-sulfoximine (BSO)-induced human neuron cell death with an ethanolic extract of *C. asiatica*, protected the neuronal cells against oxidative stress.

10. *ACORUS CALAMUS*

Acorus calamus, known as “sweet flag” or “calamus” is a semiaquatic, perennial, aromatic herb from the Acoraceae family which is abundant in subtropical swampy or marshy habitats of Asia, North America, and Europe. The essential oil contained in the leaves and rhizomes of *A. calamus* have a range of biological activities that have been exploited in the treatment of various disease states. It is also used as rejuvenator for the brain and nervous system (74).

Several antiepileptic drugs exhibit analgesic clinical effectiveness against neuropathic pain. In the case of the frequently adopted pentylenetetrazole (PTZ)-induced rodent convulsion model for epilepsy, there are thought to be two underlying mechanisms involved. Primarily, convulsions induced by PTZ are regarded as being mediated through inhibition of gamma amino butyric acid (GABA) pathways in the CNS, or secondly, by increasing central noradrenergic activity. In regard to these assumptions, Jayaraman et al., reported an increase in onset latency and a reduction in PTZ-induced seizure duration in response to administration of *A. calamus* root. This outcome was rationally ascribed to a possible involvement of GABA-ergic or noradrenergic pathways in the activity of the herb (75).

During pathological conditions, oxidative stress and neuroinflammatory processes contribute to behavioral and memory impairment. Recently, Esfandiari et al., reported that *A. calamus* was dose-dependently effective in preventing inflammation in a lipopolysaccharide (LPS) model of neuroinflammation which may subsequently augment Aβ peptide production and tau protein phosphorylation. The highest dose of an *A. calamus* aqueous fractional extract (600 mg/kg) demonstrated the most improved performance in a passive avoidance memory test as well as the lowest stress level in the elevated plus maze model. In addition, oxidative stress markers including superoxide dismutase, glutathione peroxidase and total antioxidant activity in hippocampal samples of *A.* calamus-treated cells were decreased along with lower malondialdehyde (MDA) levels compared to controls (76).

Since Aβ peptide stimulates neuronal apoptosis in the brain and primary neuronal cultures, Geng et al., studied the activity of β-asarone, an important chemical constituent of the acoraceae family, on cognitive function and neuronal apoptosis in Aβ-hippocampally injected rats. The results showed that $A\beta_{1\text{-}42}$-induced neuronal apoptosis in the hippocampus was hindered by β-asarone through up-regulation of Bcl-2, Bcl-w, caspase-3 activation, and JNK phosphorylation (77). β-asarone exhibits suppressive activity on pro-inflammatory mediators via NF-κB signaling and the JNK pathway in activated microglial cells. It also prevents an LPS-induced increase in JNK phosphorylation in a concentration dependent manner. Inhibition of JNK reduces LPS-provoked activity of COX-2, TNF-α and IL-6, which are key cytokines in cerebral inflammation and neurodegeneration. Since COX-2 is the effector of JNK-mediated neurotoxic degeneration of

dopaminergic neurons, β-asarone may represent a putative therapy against neuroinflammatory disease (78).

The inhibitory effect of a hydroethanolic extract of *A. calamus* rhizome on oxidative stress-induced changes is achieved by clearing free radicals and upgrading the levels of antioxidant. Thus, increased striatal glutathione (GSH) content and glutathione-S-transferase (GST) activity along with decreased dopamine receptor density, suggests that the neurotoxic behavioural changes produced by acrylamide may be prevented following administration of *A. calamus* (79). It has also been reported that *A. calamus* extract mediates neuroprotection by reducing lipid peroxidation, glutathione levels and superoxide dismutase (SOD) activity after middle cerebral artery occlusion-induced ischaemia in rats (80). It is a combination of such antioxidant, neuroprotective and neurotransmitter function modifying activities of *A. calamus* that underlies its traditional use in individuals on the autism spectrum (42).

11. *GINKGO BILOBA*

Ginkgo biloba extract is a remedy that has presented promising outcomes in treating a wide variety of circulatory, brain and nerve health problems. The most common studies concerning *G. biloba* on neurological issues have focused on memory enhancement, arterial dementia, Alzheimer's disease and behavioral disorders. Use of *G. biloba* alongside psychiatric drugs either tends to strengthen their effect or decrease their side effects (81, 82). Flavonoids and terpenoids with antioxidant, anti-inflammatory and neuroprotective effects are the primary therapeutic constituent elements of *G. biloba* extract. Ginkgo also has beneficial effects on cognitive and neurological performance and this stems from antioxidant activity, arterial regulation, and platelet-activating factor antagonism to protect the brain from ischemic damage. *G. biloba* extract can modify several central nervous system and neurotransmitter functions. In accord with this, oral administration of *G. biloba* extract in rats has been shown to evoke an initial decrease in the concentration of the noradrenaline metabolite normetanephrine in the cerebral cortex. Subsequently, this initial effect was superseded by a raised normetanephrine level that was apparent up to two weeks later. This longer term *G. biloba* treatment however, led not only to a reduced cortical β-adrenoceptor density but also diminished β-adrenoceptor-stimulated adenylate cyclase activity (83). A later investigation corroborated the decrease in β-adrenoceptors in the frontal cortex as well as the hippocampus in response to 7-day oral treatment with extract of *G. biloba* (84). The findings of both of these studies were thought to signify an important β-adrenergic system involvement in the therapeutic activity of *G. biloba* on learning and memory.

In an investigation using a mouse model (85), an extract of *G. biloba* (EGb 761) was described as having a protective effect against MPTP-induced nigrostriatal dopaminergic neurotoxicity and it was deduced that inhibition of monoamine oxidase in the brain may have been responsible for this neuroprotective outcome (85). Likewise, in another study, the striatal dopaminergic neurotoxicity of MPTP delivered subcutaneously by osmotic minipumps was inhibited by 17-day

dosing with *G. biloba* extract. It was highly noteworthy that this inhibitory counteractive response was independent of neurotoxic MPTP uptake by dopamine neurons (86).

Bilobalide, a sesquiterpenoid lactone present in *G. biloba*, reportedly inhibits rat hippocampal NMDA-induced choline efflux after phospholipase A_2 stimulation and membrane degeneration both *in vitro* and *in vivo* studies (87). In a comparable investigation, hypoxia has also been shown to release choline from rat hippocampal slices in a bilobalide reversible manner (88). Hence it might be hypothesized from the outcomes of such research, that bilobalide would have a potentially favorable action against the sequalae of hypoxia or excitotoxicity.

G. biloba has proven to be a commonly employed herb for treating age-related memory loss and there are a number of reports on its memory improving impact (89). The aging process is responsible for oxidative damage to DNA, protein, lipid, and other biological macromolecules. The resultant injury radically contributes to degenerative diseases occurring in the brain, sensory and cardiovascular systems. Substantial interest in the use of antioxidants has developed with an ultimate goal of protecting cellular components from oxyradical attack, especially lipoperoxidation (90). It has been revealed that acute treatment with *G. biloba* extract reduced α_2-adrenoceptor binding density in the hippocampus and cerebral cortex of aged versus young rats. In contrast, chronic administration of Gingko extract actually elevated α_2-adrenoceptor binding in aged animals, so it appears that noradrenergic activity in older rats is more prone to *G. biloba* exposure (91). Nonetheless, these findings should be considered in view of the extended Gingko enhancing effect on normetanephrine level, but also with the diminished cortical β-adrenoceptor density plus adenylate cyclase activity mentioned earlier (83).

Ovariectomy (OVX) in female rats combined with chronic stress restraint has been reported to create cognitive dysfunction along with hippocampal CA3 neuronal damage. Administration of Ginkgo biloba extract in these OVX/stressed animals improved both the memory impairment and hippocampal neuronal loss. Based on the outcome of this research work, it was speculated that Gingko had neuroprotective and cognitive enhancing properties at the postmenopausal stage of life (92).

In humans, a clinical trial on *G. biloba* extract combined with risperidone in children aged 4-12 years, did not disclose any change in treatment outcome on their ASD, although further studies were recommended in order to further validate the result (93). Nevertheless, in an earlier small observational study of 4-weeks duration, administration of *G. biloba* extract unveiled a degree of improvement in ADS symptoms (94) suggesting that the medicinal herb may have encouraging possibilities in this condition.

CONCLUSION

A rise in the incidence of autism in recent years may point to environmental risk variables (95) though environmental factors may interact with genetic vulnerabilities (96). Although the exact relationship between autism and oxidative stress is not clear, different studies have shown that oxidative stress plays a key role in various diseases, especially those related to the nervous system (97). In individuals with ASD, numerous trials have already shown changes in antioxidants including catalase, glutathione peroxidase, and superoxide dismutase. In addition, modified concentrations of homocysteine/methionine and glutathione, as well as neuroinflammation, excitotoxicity, immune and mitochondrial dysfunction have been recorded in ASD. Genetic and environmental factors may intensify oxidative stress vulnerability (98) and a heightened oxidative stress status in autism may lead to exacerbation of the condition. In the context of this notion, all autism-effective medicinal crops possess conspicuous antioxidant activity which combined with anti-inflammatory activity and effects on neurotransmitters can be potential factors in ameliorating the symptoms of ASD.

LIST OF ABBREVIATIONS

AChEI = Acetylcholinesterase Inhibitor

AD = Alzheimer's disease

APP = Amyloid Precursor Protein

AA = Asiatic Acid

ADHD = Attention Deficit Hyperactivity Disorder

ASD = Autism spectrum disorder

BDNF = Brain Derived Neurotrophic Factor

BChE = Butyrylcholinesterase

CREB = cAMP Response Element-Binding Protein

COMT = Catechol-O-methyltransferase

CA = Centella asiatica

ETC = Electron Transport Chain

Fmri = Functional Magnetic Resonance Imaging

GABA = Gamma Amino Butyric Acid

GAD = Glutamic Acid Decarboxylase

GPX = Glutathione Peroxidase

GSH = Glutathione

GST = Glutathione-S-Transferase

IL = Interleukin

LPS = Lipopolysaccharide

MDA = Malondialdehyde

MAO = Monoamine Oxidase

MPTP = 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine

NGF = Nerve Growth Factor

NT = Neurotrophin

OVX = Ovariectomy OS = Oxidative Stress

PTZ = Pentylenetetrazole

PLA = Phospholipase A

PUFA = Polyunsaturated Fatty Acids

PET = Positron Emission Tomography

ROS = Reactive Oxygen Species

SSRIs = Selective Serotonin Reuptake Inhibitors

SOD = Superoxide Dismutase TNF = Tumour Necrosis Factor

Conflict of interest

The authors confirm that this article content has no conflict of interest.

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